OCULAR MANIFESTATIONS OF MYASTHENIA GRAVIS*

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SINCE Willis first described myasthenia gravis in the seventeenth century, increasing numbers of cases have been reported. It is not a rare disease, for several large series of cases have appeared in the literature. Rarely, however, are the manifestations confined to the eyes. Such a case forms the basis of this report. To facilitate the explanation of these manifestations, a brief review of the subject is presented.

Pathology.—Myasthenia gravis is characterized by an increased muscular fatiguability with a tendency to relapses and remissions. The fatiguability may be confined to, or predominant in, a particular group of muscles for a lengthy period. The most constant pathological changes are collections of small lymphocytic cells between the muscle cells, called "lymphorrhages". They may be present in muscles which do not exhibit myasthenia and are not always found in muscles which do show myasthenia clinically. They may also occur in organs such as the liver, spleen, kidneys and pancreas. The thymus gland is enlarged in about 50% of cases. The enlargement may be due to hyperplasia or a true neoplasm. A constant change is an infiltration of the thymus with lymphocytes.

Etiology.—The cause of myasthenia gravis is explained by the theory of neurohumoral transmission of nervous impulses. In 1921, Otto Loewi suggested that a chemical substance might be responsible for the transmission of a nervous impulse across a synapse in the autonomic nervous system. In 1936, Dale, Feldberg and Vogt demonstrated that acetylcholine is the mediator substance for the transmission of impulses from the motor nerve ending to the voluntary muscle cell. This site is called the myoneural junction. Further work demonstrated the presence of an enzyme, cholinesterase, whose function was to hydrolyze acetylcholine into acetic acid and the very weakly acting choline. Cholinesterase is widely distributed in the blood and body tissues, and its action is very rapid. This enzyme limits the site of action of acetylcholine and also limits the duration of action of acetylcholine to a very brief period. When cholinesterase is inactivated, the action of acetylcholine is prolonged and intensified. The enzyme may be inactivated by physostigmine and by prostigmine.

Acetylcholine is the mediator substance between parasympathetic nerve fibres and their effector cells, namely, smooth muscles and glands. When acetylcholine is injected into the body, it stimulates smooth muscle cells and gland cells directly. In this respect it resembles the alkaloid muscarine and has been called the "muscarinic" actions of acetylcholine. Acetylcholine also stimulates autonomic ganglion cells in low concentrations and depresses them in high concentrations. In these actions, it resembles the alkaloid nicotine. Furthermore, both nicotine and acetylcholine have similar effects on skeletal muscles. For these reasons, the stimulating actions of acetylcholine on autonomic ganglion cells and on skeletal muscle cells, have been termed nicotinic. Atropine blocks only the muscarinic actions of acetylcholine. Curare blocks only the nicotinic actions.

In 1857 Claude Bernard found that mild curare poisoning will block impulses passing from nerve to skeletal muscle when both are capable of functioning. In 1934, Walker reported a case of myasthenia gravis with lid ptosis and weakness of the bulbar muscles. At that time it was thought that myasthenia gravis was due to a curare-like poisoning at the myoneural junction. Since physostigmine was known to be a partial antagonist to curare, Walker administered physostigmine to this patient. This resulted in a temporary improvement in the patient's symptoms, the improvement increasing with increase in the dose of physostigmine up to gr. 1/45, by injection. However the patient felt faint and trembled with this large dose. Then Walker considered the use of prostigmine, a drug similar in action to physostigmine. In 1935, Walker showed before the clinical section of the Royal Society of Medicine, two cases in which the most dramatic and complete relief of symptoms had been produced repeatedly by prostig-

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mine. These findings were confirmed by Pritchard in the same year. From these observations has evolved the theory that in myasthenia gravis there is a deficiency of acetylcholine at the myoneural junction. Prostigmine inactivates cholinesterase and allows acetylcholine to accumulate and act over a longer period.

A subcutaneous injection of 0.5 to 1.5 mgm. of prostigmine methylsulphate and 0.6 mgm. of atropine sulphate forms a diagnostic test for myasthenia gravis. The principal results are the rapid removal of weakness of the skeletal muscles involved and a feeling of general well-being. The atropine is added to overcome the muscarinic effects such as pallor, sweating, diarrhœa and general collapse.

The clinical picture.—Clinically the onset is usually gradual. The increased muscular fatiguability is most frequently first observed in the ocular muscles. Walsh stated that 25% of his series of 63 cases consulted an ophthalmologist first. Ptosis of one or both upper lids is the first symptom in over 50% of cases. Ptosis is soon associated with a varying degree of diplopia. Less often the bulbar muscles are first involved. The patient will complain of difficulty in swallowing or talking. Occasionally the symptoms are generalized at the onset. Characteristically the symptoms appear in the evening when the patient is tired, and disappear after the patient has rested during the night.

On examination unilateral or bilateral ptosis is seen frequently. Ptosis occurred in 54 of Walsh's series of 63 cases. Weakness of the orbicularis oculi may occur. Hence there may be both ptosis and inability to close the eyelids voluntarily. Weakness of the external ocular muscles is asymmetrical. One or all of the muscles may be involved and many combinations may occur. The picture may vary from day to day from a slight weakness to a total external ophthalmoplegia. Occasionally conjugate ocular movements appear to be affected, but more often there is no functional relationship between the muscles involved in the two eyes. Rarely there may be abnormal associated movements of the lids similar to those occurring as a result of misdirection of regenerated nerve fibres of the oculomotor nerve. Œdema of the lids is a rare prodromal sign, as is also retraction of the upper lid. The internal muscles of the eye are not involved and hence the pupillary light reflexes are normal. Paresis of accommodation is rare. Visual acuity and visual fields are not altered. A case of myasthenia gravis may manifest itself only by its ocular signs and symptoms; it is then a case of purely "ocular" myasthenia gravis. Rarely it may remain as such. More frequently it will progress to involve other skeletal muscles, even after having been confined to the eye muscles for as many as twenty-five years.

The diagnosis rests upon demonstrating increased muscular fatiguability, by such movements as repeated opening and closing of the eyes to reveal a ptosis, or by repeated movements of the eyes in certain directions to bring on diplopia. The diagnosis may be confirmed by the response to prostigmine and atropine as outlined above. Walsh reports that in all of his cases with ptosis, improvement in levator action was evident after using 1.5 mgm. of prostigmine subcutaneously. The muscles attached to the eyeball are more resistant to prostigmine therapy than other skeletal muscles. Hence more than 1.5 mgm. of prostigmine may be required to improve ocular motility. Otherwise the diagnosis may be obscure. Failing the response to prostigmine, one may use quinine or curare. Both drugs increase the symptoms of myasthenia by blocking the transmission of the impulse at the myoneural junctions of skeletal muscles. In an adult one or two doses of 0.6 gm. of quinine will almost always suffice. Other diseases respond to parenteral prostigmine, such as amyotrophic lateral sclerosis, bulbar palsy, and some of the muscular dystrophies. The response, however, is minimal, ordinarily less than 5% and never over 10% of the effect seen in patients with myasthenia gravis.

CASE REPORT

The patient was a white male, 57 years old. He was first seen on admission to the Toronto Western Hospital on December 9, 1946. His complaints were a sudden onset of increasing diplopia for the past three weeks and drooping of the right upper lid for the past five days.

The patient was last in his usual state of good health three weeks before admission. He had had no complaints referable to the eyes and had been wearing a correction for close work. At that time he noted that he could not file metal objects properly because of blurred vision. This blurring progressed to double vision, one image being above the other. The diplopia increased rapidly and the patient was obliged to cease working five days later. About two weeks after the onset the right upper lid began to droop and very quickly progressed to the point where it obstructed his vision. There had been no previous episodes similar to the present one. He had no difficulty in chewing, swallowing, talking or breathing. He did not complain of any weakness of his limbs. Functional enquiry was essentially negative.

Physical examination was negative except for the ocular signs. His visual acuity was 20/20 in each eye with correction. The right eye showed a complete ptosis. The eye was abducted. There was inability to rotate the eye upwards, medially or downwards. The left eye showed normal levator action and movements of the globe were full. In both eyes, orbicularis action was present, there was no nystagmus, and corneal sensation was normal. There was no convergence. The pupils were round, equal, 3 mm. in diameter and reacted briskly to light directly and consensually. The media were clear; the fundus examination was negative. Peripheral and central fields were normal. Laboratory investigation revealed a normal blood picture, normal urine, normal roentgenograms of skull and chest, and normal spinal fluid.

A diagnosis of right external ophthalmoplegia was made. The causes considered were syphilis, neoplasm, toxæmia and cerebrovascular accident.

On the following day there were abnormal signs in the left eye. There was a partial ptosis, the palpebral fissure being 9 mm. vertically. There was paralysis of the internal rectus, the inferior rectus and the inferior oblique. There was partial weakness of the levator, superior rectus and superior oblique. The next morning the patient was seen immediately upon awakening. He was able to raise both upper lids well above the central visual area. He had some increased movement of both

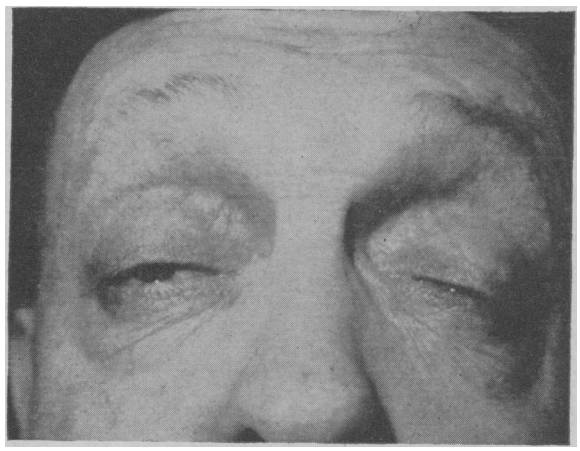

Fig. 1

eyes. However, within one and one-half minutes the upper lids gradually dropped until there was a complete ptosis on the right side and a partial ptosis on the left. A diagnosis of myasthenia gravis was considered. On December 13, he was given a diagnostic dose of 1.5 mgm. of prostigmine methylsulphate and 0.6 mgm. of atropine sulphate subcutaneously. There was no apparent reaction and the diagnosis was doubtful. The diagnostic test was repeated on another day. This time he was given 1 mgm. of prostigmine followed by 0.5 mgm. every five minutes for two doses. Within 12 minutes the patient was able to raise both lids to almost normal height. He was able to move both globes horizontally and downwards over a wide excursion. There was no upward movement. The effect was maximal at the end of 30 minutes. Two hours after the injections the lids began to droop and the eye movements began to diminish. By three and one-half hours the eyes and the lids had returned to their previous state.

The patient was then placed on a daily routine of prostigmine bromide *per os*, potassium chloride and ephedrine. This routine afforded him only intermittent periods of freedom from symptoms, lasting about fifteen minutes. To produce more continuous relief, the prostigmine was gradually increased to 360 mgm. daily. This amount resulted in good ocular motility through the day, but it also produced diarrhœa, cramps and cold sweats which were not controlled by atropine. The prostigmine was then decreased.

The patient was considered a suitable candidate for thymectomy. On February 25, 1947, thymectomy was performed. The anterior mediastinum contained an irregular fatty mass extending from the level of the fourth costal cartilage to the isthmus of the thyroid gland. It was not obviously bi-lobed nor did it contain any tumour visible or palpable. This mass was removed with relative ease. Microscopic sections revealed adipose tissue containing scattered collections of lymphocytes and an occasional Hassall's corpuscle surrounded by lymphocytes.

Shortly after the patient regained consciousness there appeared to be a definite improvement in the ocular signs. The improvement continued and was maintained. Prostigmine therapy was discontinued without adverse effect on the eighth postoperative day. Convalescence was complicated by thrombophlebitis in the right calf and also by a small serous effusion beneath the wound communicating with a similar collection of fluid in the anterior mediastinum. These complications responded rapidly to appropriate therapy. The patient was discharged on the twenty-second postoperative day. When last seen on April 11, 1947, the patient exhibited full normal range of ocular motility with normal lid elevation in each eye.

DISCUSSION

Thymectomy, ephedrine and potassium chloride have been mentioned. The presence and possible relationship of a thymus tumour in a patient with myasthenia gravis was first reported in 1901. This observation was subsequently confirmed by many writers. A few unsuccessful attempts were made to remove the thymus gland. In 1936, Blalock reported the first successful operation of total thymectomy for myasthenia gravis and eight years later he had completed 20 such operations. Keynes of London, England, has reported 51 thymectomies for myasthenia gravis since 1942. From a comparison of the results of these two surgeons, the following conclusions and approximate percentages may be drawn: (1) A thymic tumour is found in 10% of cases coming to operation. (2) The operative mortality of thymectomy is 15%. (3) Following operation, 50% are markedly improved, 35% are improved to a varying degree and 15% show no improvement. It must be emphasized here that both Blalock and Keynes have avoided operation on patients with mild symptoms almost completely controlled with the aid of prostigmine, and that the operation was not denied to those with severe symptoms who were very poor operative risks.

Following thymectomy the patient herein reported appears cured. However it is possible that the disease has undergone a natural remission. Hence a critical decision on the value of

the thymectomy cannot be made until more time has elapsed.

Edgeworth, herself a victim of myasthenia gravis, accidentally discovered that ephedrine afforded her some symptomatic relief. Ephedrine increases skeletal muscle power in myasthenia, but the mechanism of action is unknown. Its effectiveness is about 10 to 15% of that of prostigmine. Ephedrine is a useful adjunct to prostigmine therapy. Potassium chloride has a mild beneficial effect. There is some experimental evidence that potassium ions strongly sensitize ganglion cells to acetylcholine. Furthermore Brown and Feldberg suggest that the discharge of acetylcholine may be effected by potassium ions mobilized in the passage of the nerve impulse. In 1935, with these data in mind, Laurent and Walther reported that potassium chloride in large doses produced demonstrable improvement in myasthenia gravis. It produces disagreeable symptoms when taken by mouth in effective doses. At present, potassium chloride is also a useful adjunct to prostigmine therapy.

CONCLUSIONS

1. The manifestations of myasthenia gravis may be confined to the eyes and adnexa.

2. The muscles attached to the globe are resistant to prostigmine therapy. A dose greater than 1.5 mgm. of prostigmine may be required to produce a positive response for diagnostic purposes.

3. Myasthenia gravis should be included in the differential diagnosis of external ophthalmoplegia.

4. The exact relationship of the thymus to myasthenia gravis is unknown. However a patient with this disease may benefit from thymectomy.

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AN ASSESSMENT OF THE RESULTS OF VAGOTOMY*

(Based upon personal experience of 66 cases.)

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IT is now about two years since we started doing vagotomies, and with an experience of 66 cases I feel it may be possible to pass judgment upon some of the results, even though sufficient time has not elapsed to permit anyone to guess what remote problems may yet develop.

Vagotomy abolishes the pain of ulcer, reduces the total volume of gastric secretion, brings about a state of achlorhydria and permits the inhibitor sympathetic nervous system to act unopposed upon the gastro-intestinal musculature, the augmentor having been severed.

The transabdominal route has met with almost universal acceptance as being more easily accomplished by the ordinary surgeon doing gastro-intestinal work. The original controversy as to the respective merits of transthoracic versus transabdominal routes has been settled in favour of the latter. There may be, however, isolated instances where an approach through the thorax may still be advantageous. Chest surgeons, loath to relinquish an operation of considerable simplicity, loudly proclaim its advantages, but the abdominal visual verification of the existence of disease, and the performance of other necessary surgical procedures weigh too heavily against it as an elective routine procedure.

For some time after Dragstedt's introduction of modern vagotomy, it was considered necessary to check the completeness of the operation by a gastric analysis done in hypoglycæmic states subsequent to the exhibition of insulin sufficient to cause the blood sugar level to fall below fifty. This proved frequently to be something of an ordeal, nevertheless, we faithfully carried this out on our first 23 cases. Twenty-two of these showed complete achlorhydria throughout the entire two-hour test period, the odd case showing a free acid of ten units on the fourth reading. We have in consequence abandoned this procedure, believing that vagotomy, thoroughly carried out, means complete subsequent achlorhydria of the neurogenic phase,

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